# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**75-684**

## ADMINISTRATIVE DOCUMENTS

**APPROVAL SUMMARY / REVIEW OF PROFESSIONAL LABELING**
**DIVISION OF LABELING AND PROGRAM SUPPORT / LABELING REVIEW BRANCH**

ANDA Number: 75-684 Date of Submission: 2/16/01, 3/26/01, and 4/2/01

Applicant's Name: Bedford Laboratories

Established Name: Famotidine Injection 10 mg/mL, 50 mL Pharmacy Bulk Package

**APPROVAL SUMMARY** (List the package size, strength(s), and date of submission for approval):

- Do you have 12 Final Printed Labels and Labeling? YES
- Carton: Satisfactory in FPL (2/16/01)
- Container Labels: Satisfactory in FPL (2/16/01)
- Professional Package Insert Labeling: Satisfactory in FPL (4/2/01)
- Revisions needed post-approval: YES

**BASIS OF APPROVAL:**

| | |
|---|---|
| • Was this approval based upon a petition? | NO |
| • What is the RLD on the 356(h) form: | PEPCID |
| • NDA Number: | 20-249 |
| • NDA Drug Name: | Pepcid |
| • NDA Firm: | Merck |
| • Date of Approval of NDA Insert and supplement #: | March 14,2001; S-012 |
| • Has this been verified by the MIS system for the NDA? | YES |
| • Was this approval based upon an OGD labeling guidance? | NO |
| • Basis of Approval for the Container Labels: | Side by Side |
| • Basis of Approval for the Carton Labeling: | Side by Side |

**FOR THE RECORD:**

1. Review based on the labeling of NDA 19-510/S-029 and NDA 20-249/S-012, approved March 14, 2001, draft labeling of Marsam's bulk famotidine injection.
2. Patent/ Exclusivity:
   - Firm cites Paragraph III certification for U.S.Patent No. 4,283,408 which expires April 15, 2001.
   - No exclusivity currently granted for these products.
3. Storage Conditions: NDA – $2^0$ - $8^0$ ($36^0$-$46^0$F); ANDA - $2^0$ - $8^0$C($36^0$ - $46^0$F)
   - USP - "Preserve in well-closed containers, protected from light."
4. Product Line:
   - The innovator markets their product in 2 mL single dose vial and 4 mL and 20 mL multidose vials.
   - The applicant proposes to market their product in 2 mL single dose vial 4 mL two-dose vial and 20 mL multidose vial and this 50 mL Pharmacy Bulk Package.
5. Inactive Ingredients:
   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 76 (Volume 1.1)
6. Container/Closure: see page 267.
   50 mL vial – Container: 100 cc vial
   Closure: 20 mm/gray liquid/siliconized stopper
7. It was decided that the usual dose, 20 mg/2 mL, should be included along with the total volume of expression as a secondary expression since the reference listed drug always puts the volume/strength in terms of the usual dose for this product.

Date of Review: April 9, 2001 Date of Submission: 2/16/01, 3/26/01, and 4/2/01

Primary Reviewer: Koung Lee KL Date: 04/10/01

Team Leader: Charlie Hoppes Date:

cc:

ANDA 75-684

JAN 24 2001

Bedford Laboratories
Attention: Shahid Ahmed
270 Northfield Road
Bedford, Ohio 44146

Dear Sir:

This is in reference to your abbreviated new drug application dated July 30, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Famotidine Injection, 10 mg/mL, supplied in 50 mL Pharmacy Bulk Packages.

Reference is made to your amendments dated November 3, December 1, and December 22, 2000.

We have completed the review of this abbreviated application and have concluded that based upon the information you have presented to date, the drug is safe and effective for use as recommended in the submitted labeling. Therefore, the application is **tentatively approved.** This determination is based upon information available to the Agency at this time, (i.e., information in your application and the status of current good manufacturing practices (CGMP) of the facilities used in the manufacture and testing of the drug product). Please note that this decision is subject to change on the basis of new information that may come to our attention.

The reference listed drug product (RLD) upon which you have based your application, Pepcid Injection of Merck Research Laboratories, is subject to a period of patent protection (U.S. Patent No. 4,283,408. Your application contains a Paragraph III Certification to this patent under Section 505(j)(2)(A)(vii)(III) of the Act stating that you will not market this drug product prior to patent expiry. Therefore, final approval of this application may not be made effective pursuant to 21 U.S.C. 355 (j)(5)(B)(ii) of the Act until this patent has expires, i.e., currently April 15, 2001.

Because the agency is granting a tentative approval to this application, please submit an amendment at least 60 days prior to the date you believe your application will be eligible for final approval. This amendment should identify changes, if any, in the conditions under which the product was tentatively approved, and should include updated information such as final printed labeling, chemistry, manufacturing, and/or controls data as appropriate. In order to reactivate your application prior to final approval, an amendment should be submitted even if none of these changes were made. This amendment should be designated clearly in your cover letter as a MINOR AMENDMENT. In addition to this amendment, the Agency may request at any time prior to the final date of approval that you submit an additional amendment containing the information described above.

Failure to submit either amendment may result in rescission of the tentative approval status of your application, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this abbreviated application, as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (CGMPs) are subject to agency review before final approval of the application will be made.

Please note that this drug product may not be marketed without final Agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under Section 501 of the Act and 21 U.S.C. 311(d). Also, until the Agency issues the final approval letter, this drug product will not be deemed approved for marketing under 21 U.S.C. 355 and will not be listed in the "Approved Drug Products with Therapeutic Equivalence Evaluations" list (the "Orange Book"), published by the Agency. Should you believe that there is a basis for issuing the final approval letter prior to April 15, 2001, you should amend your application accordingly.

If you have questions concerning the status of this application, please contact Kassandra Sherrod, R.Ph., Project Manager, at (301) 827-5849.

Sincerely yours,

Gary Buehler 1/24/01
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

**TENTATIVE APPROVAL SUMMARY**
**REVIEW OF PROFESSIONAL LABELING**
**DIVISION OF LABELING AND PROGRAM SUPPORT**
**LABELING REVIEW BRANCH**

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ANDA Number: 75-684 Date of Submission: November 3, 2000

Applicant's Name: Bedford Laboratories

Established Name: Famotidine Injection 10 mg/mL, 50 mL Pharmacy Bulk Package

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**APPROVAL SUMMARY** (List the package size, strength(s), and date of submission for approval):

- Do you have 12 Final Printed Labels and Labeling? YES
- Container Labels: Satisfactory in FPL (11/3/00)
- Professional Package Insert Labeling: Satisfactory in FPL (11/3/00)
- Revisions needed post-approval: YES

INSERT

a. DESCRIPTION

Revise the last sentence to read "...restricted to the preparation of intravenous solution."

b. INDICATIONS AND USAGE

Add "adult" between "Most" and "patients" in the second statement in the first indication.

c. PRECAUTIONS

Replace the subsection headings "*Pediatric Patients*" and "*Use in Elderly Patients*" with "*Pediatric Use*" and "*Geriatric Use*", respectively.

d. DOSAGE AND ADMINISTRATION

i. *Dosage for Pediatric Patients*

Revise the first statement to read "See PRECAUTIONS, *Pediatric Use*." and revise the following sentence to read "The studies described in PRECAUTIONS, *Pediatric Use* suggest..."

ii. *Preparation of Solutions*

(a) Add the following as the second sentence in the first paragraph.

Information regarding the preparation of intravenous solutions, *not* for infusion, is for informational purposes only.

(b) Add the following to the second to the last paragraph.

[For informational purposes only]

The above comments will be communicated to the firm by the labeling reviewer via telephone soon after the application is tentatively approved.

**BASIS OF APPROVAL:**

- Was this approval based upon a petition? NO
- What is the RLD on the 356(h) form: PEPCID
- NDA Number: 20-249

- NDA Drug Name: Pepcid
- NDA Firm: Merck
- Date of Approval of NDA Insert and supplement #: March 18, 1999;S-009
- Has this been verified by the MIS system for the NDA? YES
- Was this approval based upon an OGD labeling guidance? NO
- Basis of Approval for the Container Labels: Side by Side
- Basis of Approval for the Carton Labeling: Side by Side

**FOR THE RECORD:**

1. Review based on the labeling of NDA 19-510/S-026 and NDA 20-249/S-009, Issued November 1998; approved March 18, 1999, and the tentatively approved on December 23, 1998, draft labeling of Marsam's bulk famotidine injection.
2. Patent/ Exclusivity:
   - Firm cites Paragraph III certification for U.S.Patent No. 4,283,408 which expired October 15, 2000.
   - Pediatric Exclusivity expires April 15, 2000.
3. Storage Conditions:
   - NDA – $2^0$ - $8^0$ ($36^0$-$46^0$F)
   - ANDA - $2^0$- $8^0$C($36^0$ - $46^0$F)
   - USP - "Preserve in well-closed containers, protected from light."
4. Product Line:
   - The innovator markets their product in 2 mL single dose vial and 4 mL and 20 mL multidose vials.
   - The applicant proposes to market their product in 2 mL single dose vial 4 mL two-dose vial and 20 mL multidose vial and this 50 mL Pharmacy Bulk Package.
5. Inactive Ingredients:
   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 76 (Volume 1.1)
6. Container/Closure: see page 267.
   50 mL vial – Container: 100 cc vial
   Closure: 20 mm/gray liquid/siliconized stopper
7. It was decided that the usual dose, 20 mg/2 mL, should be included along with the total volume of expression as a secondary expression since the reference listed drug always puts the volume/strength in terms of the usual dose for this product.

Date of Review: December 19, 2000 Date of Submission: November 3, 2000

Primary Reviewer: Koung Lee Date: 12/21/00

Team Leader: Charlie Hoppes Date:

cc:

1/4/01

LABELING

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-684 Date of Submission: February 28, 2000

Applicant's Name: Bedford Laboratories

Established Name: Famotidine Injection 10 mg/mL, 50 mL Pharmacy Bulk Package

Labeling Deficiencies

1. CONTAINER

   a. Relocate "NOT" to the second line in the Boxed statement on the principal display panel.

   b. Replace "FOR THE PREPARATION OF IV SOLUTIONS." with "MUST BE DILUTED PRIOR TO I.V. USE" and "Do not dispense as a unit" on the principal display panel.

   c. Add "Once the container closure has been punctured, withdrawal of the container contents should be completed without delay. THE ENTIRE CONTENTS OF THE VIAL SHOULD BE DISPENSED WITHIN 4 HOURS OF INITIAL ENTRY."

   d. Add "Date Entered:_____" and "Time of Entry:_____"

2. CARTON

   See CONTAINER comments (b) and (c).

3. INSERT

   a. DESCRIPTION

      i. Revise the first sentence of the third paragraph to read as, "...for intravenous injection after dilution."

      ii. Revise the third paragraph to read as "...Water for Injection q.s. 1 mL, and benzyl alcohol 0.9% added as preservative."

   b. CLINICAL PHARMACOLOGY IN PEDIATRIC PATIENTS

      In the first row under "Effect[a]" in Table 8, revise to read as, "gastric pH > 3.5 for 8.7 ± 4.7[b] hours".

   c. INDICATIONS AND USAGE

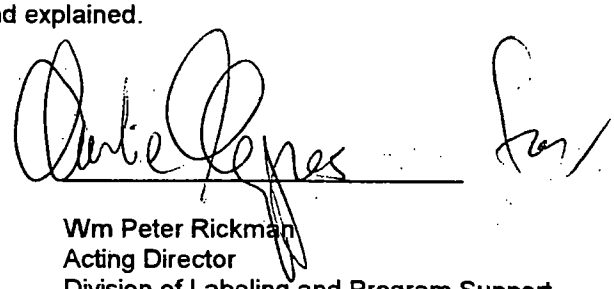
      Revise the first sentence of the first paragraph to read as, "...solution for intravenous injection after solution, is intended for..."

Please revise your labeling as instructed above and submit 4 copies of draft labels and carton and package insert labeling for a tentative approval or 12 final printed copies of labels and labeling for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other factors (print size, prominence, etc.) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes –

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.



Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-684 Date of Submission: July 30, 1999

Applicant's Name: Bedford Laboratories

Established Name: Famotidine Injection 10 mg/mL, 50 mL Pharmacy Bulk Package

Labeling Deficiencies:

1. CONTAINER (50 mL)

   a. Add the usual dose for this product, "20 mg/2 mL", as the secondary expression of strength underneath the total volume expression of strength.

   b. Add "MUST BE DILUTED PRIOR TO I.V. USE" and "Do not dispense as a unit".

3. CARTON

   See CONTAINER comments a. and b.

4. INSERT

   a. INDICATIONS AND USAGE

      i. Add "in adults" between "studies" and "have" for the second indication.

      ii. Add "adults" between "Most" and "patients" in the first sentence of the third indication.

   b. CONTRAINDICATIONS

      Add the following:

      "Cross sensitivity in this class of compounds has been observed. Therefore, famotidine should not be administered to patients with a history of hypersensitivity to other $H_2$-receptor antagonists."

   c. PRECAUTIONS (Pediatric Patients)

      Add the following as the third to the last sentence of the first paragraph:

      "Similarly, in pediatric patients 1 to 15 years of age, intravenous doses of 0.5 mg/kg were associated with a mean AUC similar to that seen in adults treated intravenously with 40 mg."

   d. ADVERSE REACTIONS

      Revise the first sentence of the last paragraph to read as "...may also occur with famotidine for oral suspension, famotidine orally disintegrating tablets, famotidine preservative free in plastic container and famotidine injection.

   e. DOSAGE AND ADMINISTRATION

      i. Dosage Adjustments for Patients with Severe Renal Insufficiency

         Add "adult" between "In" and "patients" in the first sentence of the first paragraph.

ii. Relocate "Preparation of Solutions" subsection just before the "Concomitant Use of Antacids" subsection and switch directions 1 and 2.

iii. Add the following as the second to the last and last paragraph to the "Preparation of Solutions" subsection.

> To prepare famotidine intravenous solutions, aseptically dilute 2 mL of Famotidine Injection (solution containing 10 mg/mL) with 0.9% Sodium Chloride Injection or other compatible intravenous solution (see Stability, Famotidine Injection) to a total volume of either 5 mL or 10 mL and inject over a period of not less than 2 minutes.
>
> To prepare famotidine intravenous infusion solutions, aseptically dilute 2 mL of Famotidine Injection with 100 mL of 5% dextrose or other compatible solution (see Stability, Famotidine Injection), and infuse over a 15 to 30 minute period.

iv. Stability

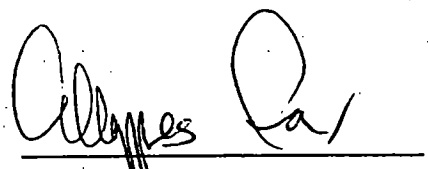
Relocate the last paragraph under the "Preparation of Solutions" subsection to be the first paragraph of this subsection.

Please revise your labels and labeling as instructed above and submit 4 draft container labels and carton and package insert labeling for a tentative approval or 12 final printed copies of label and labeling for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other factors (print size, prominence, etc.) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes –

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.



Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 75-684

Bedford Laboratories
A Division of Ben Venue Laboratories, Inc.
Attention: Shahid Ahmed
270 Northfield Road
Bedford, OH 44146

SEP 24 1999

Dear Sir: -

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Famotidine Injection, 10 mg/mL, 50 mL vial, Pharmacy Bulk Package

DATE OF APPLICATION: July 30, 1999

DATE (RECEIVED) ACCEPTABLE FOR FILING: August 03, 1999

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Kassandra Sherrod
Project Manager
(301) 827-5848

Sincerely yours,

for

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research